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| EXAMINER | |
|---|---|
| STAPLES, MARK | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/547,669 | CALISTRI ET AL. | |
| | Examiner | Art Unit | |
| | Mark Staples | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06/29/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2 and 4-22* is/are pending in the application.

4a) Of the above claim(s) *7 and 12-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8-11 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicants' amendment of claims 1, 2, and 4-12; cancellation of claim 3; and submission of new claims 13-22 in the paper filed on 06/29/2007 is acknowledged.

It is noted that election/restriction requirement was made final in the Office Action mailed on 03/28/2007.

Newly submitted claims 13-21 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims recite new primers of SEQ ID NOs: 11 and 12 which are patentably distinct species from the originally elected primers. Claim 20 recites a kit which is distinct from the currently elected methods.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 13-21 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

2. Claims 1, 2, 4-6, 8-11, and 22 restricted to SEQ ID NOs: 9, 10, 13, 14, and 15 are pending and at issue.

3. Applicants' arguments filed on 06/29/2007 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

## ***Objections and Rejections that are Withdrawn/ Moot***

4. The objection to improper use of trademarks in the specification is withdrawn in light of Applicant's amendment of trademarks to be used according to current Office guidelines.

5. The objection to claim 3 is moot in light of the Applicant's cancellation of this claim.

6. The objection to claim 8 is withdrawn in light of the Applicant's amendment of this claim to end in a period.

7. The objection to claim 10 is withdrawn in light of the Applicant's amendment of this claim to recite colorimetric.

### ***Claim Rejections Withdrawn / Moot - 35 USC § 112 Second Paragraph***

The rejections of claims 1, 2, 4-6, 8-11 under 35 USC § 112 Second Paragraph are withdrawn in light of the Applicant's amendments to recite active steps which also fulfill the determination of the presence of colorectal tumors as stated in the preamble of claim 1. The rejections of cancelled claims are moot.

However new grounds of rejection are made in view of other claim amendments.

8. The rejection of claims 3 under 35 USC § 112 Second Paragraph is moot in light of the Applicant's cancellation of this claim.

***Claim Rejections Withdrawn / Moot - 35 USC § 112 First Paragraph***

9. The rejections of claims 1, 2, 4-6, 8-11 under 35 USC § 112 First Paragraph are withdrawn in light of the Applicant's amendments to limit the methods to detection of colorectal tumors. The rejections of cancelled claims are moot.

***Claim Rejections Moot - 35 USC § 102(b) and 103(a)***

10. Applicant's arguments with respect to claims 1, 2, 4-6 and 8-11 have been considered but are moot in view of the new ground(s) of rejection.

***New Objections and Rejections Necessitated by Amendment***

***New Claim Objections***

11. Claim 22 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 22 recites the same limitation that is in step e of antecedent claim 1.

***New Claim Rejections - 35 USC § 112***

12. Claims 1, 2, 4-6, 8-11, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the presence of pre-cancerous lesions are being determined. This rejection can be overcome by deleting the phrase "or pre-cancerous lesions" from the preamble of claim 1.

***New Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 4-6, 9-11, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Shuber (WO 2001/42502, previously cited).

Regarding claims 1, 2, 5, 9, and 22, Shuber teaches a method for determining the presence of colorectal tumors in a human subject (entire reference), which comprises:

a) extracting DNA from stool samples (see p. 18, 1st paragraph: "After homogenization, nucleic acid is preferably isolated from the stool sample. . . .The extracted nucleic acids are then precipitated with alcohol. . . . Total DNA is isolated using techniques known in the art");

b) PCR amplifying at least three different DNA fragments with a length of 100 base pairs or more, using deoxynucleotide triphosphates or primers labelled with detectable markers (see p. 4, 2nd paragraph, 6th sentence: "It is preferable that, in the case of DNA, the amplification reaction is a polymerase chain reaction (PCR) . . ." ; p. 9, 2nd paragraph : "Methods of the invention also comprise conducting a series of amplification reactions at a series of different genomic loci. . . . Preferably, from about 2 to about 7 amplification reactions on about 2 to about 7 loci are used. . . . In a preferred embodiment, the target fragment lengths are 200 bp, 400 bp, 800 bp, 1.3 Kb, 1.8 Kb, and 2.4 Kb" which are more than 100 base pairs and note that 200 and 400 are between 100 and 500 base pairs as recited in instant claim 5; and p. 8, 2nd paragraph, 3rd sentence: "Labels, such as fluorescent or radioactive labels, may be used" which also applies to instant claim 2);

c) quantifying the amplified fragments (amplicons);

d) calulating the total amount of different amplicons;

e) comparing the values obtained in (d) with a reference value (for steps c, d, and e see Figures 1 through 10, where quantitation is given as "Q#", which is calculated by interpolation, as recited in instant claim 9, from a standard curve consisting of known amounts of DNA, and compared to the "NEG CONTROL" as a reference value, and in Figures 1-7 is also compared to the "POSITIVE CONTROL" as another reference value). Shuber further teaches that a total amount of amplicons, that is amplifiable nucleic acid, is indicative of disease by teaching: "As shown in those figures [11A and

11B], patients with [colorectal] cancer or adenoma have an increased yield of amplifiable DNA." (see p. 22 lines 20 and 21).

Regarding claims 4 and 6, Shuber teaches a method wherein at least 8 different DNA fragments are amplified (12 loci for amplification are taught which is at least eight, as given on p. 8, 1st paragraph, last sentence: "Preferred disease-associated loci include p53, apc, MSH-2, dcc, scr, c-myc, B-catnenin, mlh-1 , pms-I , pms-2, pol-delta, and bax").

Regarding claim 10, Shuber teaches spectrophotometric detection systems (see p. 8, 2nd paragraph, 3rd sentence: "The amounts of amplification product produced may be compared to standard amounts by any suitable or convenient means, including, but not limited to . . . machine-driven optical comparison, densitometry, . . . and other known means").

Regarding claim 11, Shuber teaches a method where the reference value is determined from healthy (normal) subjects/patients (See p. 3, 2nd paragraph, 5th sentence: "Thus, tumor cells are typically intact and routinely are shed into, for example, stool, sputum, urine, bile, pancreatic juice, and blood. Such shed cells and cellular debris contain higher integrity nucleic acids and other cellular components compared to those found in specimens obtained from a healthy patient"; and see p. 10, 2nd paragraph, 3rd sentence: "A baseline for comparison of the extent of nucleic acid amplification can be amounts of nucleic acids from known normal samples").

Although this is a new ground of rejection, Applicant's argument against the prior rejection by anticipation of Shuber is not persuasive. Applicant argues (see pp. 13 and 14 of response) that Shuber does not teach detection by fluorescence. This argument is unfounded as noted by the specific citation in the rejection of claim 1 above to p. 8, 2nd paragraph, 3rd sentence: "Labels, such as fluorescent or radioactive labels, may be used".

***New Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001) as applied to claims 1 above, and further in view of Zhou et al. (2002).

Shuber teaches as noted above.

Shuber does not specifically teach fluorescein as a fluorescent label.

Regarding claim 3, Zhou et al. teach the fluorescent label fluorescein (see 7th sentence of the section *Principles of digital SNP analysis* on p. 359).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Shuber by using the fluorescent label fluorescein as suggested by Zhou et al. with a reasonable expectation of success. The motivation to do so is provided by Zhou et al. who teach that mutations in alleles associated with colorectal tumours can be detected with fluorescein as a label (entire article, especially the section *Principles of digital SNP analysis* on p. 359). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

16. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001) as applied to claims 1 and 6 above, and further in view of Kmiec et al. (WO 2001/73002, previously cited), Kmiec et al. and Albertsen et al. (US Patent No.: 6,114,124 issued 2001, previously cited), and Buck et al. (1999, previously cited).

Shuber teaches as noted above, including amplification of APC fragments and teaches a sequence comprising SEQ ID NO: 9 (see Table 1 of Office Action mailed on 03/28/2007).

Shuber does not teach other elected sequences of instant claim 8 or sequences comprising these.

Kmiec et al. teach sequences comprising SEQ ID NO: 10 and 16, and teaches sequences comprising the sequences in primer pairs SEQ ID NOs: 13 and 14 (see Table 1 of Office Action mailed on 03/28/2007).

Kmiec et al. do not teach SEQ ID NOs: 9 and 15 or sequences comprising these.

Albertsen et al. teach a sequence comprising SEQ ID NO: 15 (see Table 1 of Office Action mailed on 03/28/2007).

Albertsen et al. do not teach SEQ ID NOs: 9, 10, 13, 14, or 16; or sequences comprising these.

Buck et al. do not teach SEQ ID NOs: 9, 10, 13, 14, 15, or 16; or sequences comprising these.

Claim 8 is rejected for SEQ ID NOs: 9, 10, 13, 14, 15, and 16, as described following. With regard to Claim 8, for primers designed for amplification of APC gene, Shuber, Kmeic et al. and Alberston et al. expressly disclose the identical nucleic acid sequences presented in SEQ ID NOs: 9, 10, 13, 14, 15, and 16 of the instant invention. It is noted that the instant primer sites of SEQ ID NOs: SEQ ID NO: 9, 10, 13, 14, 15, and 16 are contained within the sequences disclosed by Shuber, Kmeic et al. and Alberston et al.

The above described references do not specifically disclose the identical primer sequences of SEQ ID NO: 9, 10, 13, 14, 15, and 16 of the primers pairs, respectively, used in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned

as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Although this is a new ground of rejection, Applicant's argument (on pp. 14-16 of the response) against the prior obviousness rejection is not persuasive. Shuber was relied upon for teaching the detection of colectal tumors. Kmiec, Alberstsen, and Buck were not relied upon for this teaching; but were relied on for teaching of known sequences and that primers can be constructed from any region of a known sequence for successful nucleic acid amplification.

## ***References of Interest***

It is acknowledged that Applicant has submitted three references of interest pertaining to detection of colorectal cancers: [1] Calistri et al. (2004), [2] Zou et al. (2006), and [3] Ahlquist et al. (2000).

## ***Conclusion***

17. No claim is free of the prior art.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples MS
Examiner
Art Unit 1637
September 12, 2007

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
9/13/07